REMARKS

Claims 1-45 and 75 are pending in the above-referenced application. The Examiner has rejected claims 1-45 and 75. Claims 4, 7-29, and 75 are amended in this Response; claims 33 and 38-41 are canceled. Applicant respectfully submits that no new matter is presented with these amendments. Applicant reserves the right to prosecute without prejudice in a future application subject matter amended from the claims by the Amendment submitted herewith. Applicant respectfully requests consideration of the amended claims presented herein and respectfully submits that the amended claims are now in condition for allowance.

I. Rejections under 35 U.S.C. § 102. The Examiner has rejected claims 1, 3, 4, 6-11, 13, 15-18, 20, 22-29, 30, 33, 36-41, 43-45, and 75 under 35 U.S.C. § 102(b), as being anticipated by Roberts *et al.* (U.S. Patent 5,958,769, issued September 28, 1999). The Examiner maintains that Roberts *et al.* discloses a method for increasing the proliferation of various cells by administering inhibitors of p27 cyclin dependent kinase and that this method can be used on stem cells, progenitor cells, fibroblasts, myeloblasts, neurons, epithelial cells, hematopoietic progenitor cells, granulopoietic cells, and embryogenic cells. In addition, the Examiner maintains that Roberts *et al.* discloses that p27 inhibitors may be used with antagonists of p21 to increase the proportion of proliferating cells in a population. Applicant, however, disagrees that Roberts *et al.* anticipates the claimed invention, because at best Roberts *et al.* merely suggests without any enabling support that a *combination* of p27 and p21 inhibitors might be used to increase the proportion of proliferating cells in a cell population (column 8, lines 19-29).

Roberts *et al.* discloses the use of p27 cyclin-dependent kinase inhibitors to increase the proportion of dividing cells to non-dividing cells in a population (see Abstract). Later in the Specification in the "Description of the Specific Embodiments," Roberts *et al.* includes a laundry list of other protein targets thought to be important in cell cycle control, including p14, p15, p16, p18, p19, and p21, which could be inhibited in conjunction with p27 to increase the proportion of proliferating cells in a population. This list is no more than a recitation of candidates that might be interesting to assess. There is no evidence that Roberts *et al.* tried any of these combinations, and there is no evidence that the inhibition of p27 and another of the listed mitotic inhibitors would be successful in achieving the desired result. Out of the many possible combinations,

Roberts *et al.* does not point to the combination of p27 and p21 particularly, and Roberts *et al.* certainly does not enable such a combination.

Recently researchers in the field of cell cycle control have shown that different cyclin-dependent kinase inhibitors have highly distinct effects on the kinetics of cell differentiation and division. *See, e.g.,* Yuan *et al.* "*In vivo* self-renewing divisions of haematopoietic stem cells are increased in the absence of the early G1-phase inhibitor, p18INK4C" *Nat. Cell Biol.* 6(5):436-442, May 2004 (where the role of p18 in the cell cycle of haematopoietic cells is discussed); Qiu *et al.* "Regenerative Response in Ischemic Brain Restricted by p21cip1/waf1" *J.Exp. Med.* 199(7):937-45, April 2004 (where the role of p21 in neural regeneration after brain injury is discussed). For discussion of the role of p21 and p27 in cell cycle control, the Examiner is directed to the Specification (page 13, line 22-page 16, line 27; and Examples). The distinct effects of cyclin-dependent kinase inhibitors on cells is unpredictable rendering the disclosure by Roberts *et al.* lacking. Such a limited disclosure cannot anticipate the claimed invention. Therefore, the claimed invention in the present application is patentable over the generic and unenabled disclosure of Roberts *et al.*

Claims 1, 3, 30, and their dependencies recite a decrease in p21 activity and do *not* recite a decrease in *both* p21 and p27 activity. Since Roberts *et al.* does not teach or suggest, the inhibition of p21 alone, it cannot anticipate claims 1, 3, 30, or their dependencies. Applicant requests the rejection of these claims be removed.

Although Roberts *et al.* does generically suggest the inhibition of p27 and p21, it does not provide an enabling disclosure sufficient to anticipate claim 4 and its dependencies. The lack of working examples in Roberts *et al.*, in which both p21 and p27 are inhibited, and the unpredictability in this art as discussed *supra* render the reference not enabled such that one of skill in this art could not practice and use the methodology based on such a limited teaching. One of skill in this art would need more to show that the inhibition of both these kinase inhibitor proteins would be useful in achieving the desired result. Roberts *et al.* does not provide any type of description of p21 indicating why it might be useful to inhibit it in combination with p27. For example, there is no suggestion that these kinase inhibitor proteins are on the same or different cell cycle control pathways. The mere reference to p21 in a list without more also does not provide enough information to the reader that inhibiting both p21 and p27 would be successful in

achieving a proliferating cell population. In fact, research has shown that each cyclin-dependent kinase inhibitor has unique effects. *See* Cheng et al. *Science* 287:1804, 2000; Cheng *et al. Nature Med.* 6(11):1235, 2000; Qiu *et al. J. Exp. Med.* 199:937, 2004; Yuan *et al. Nat. Cell Biol.* 6:436, 2004 (These references have been included in previous IDSs submitted to the Patent Office or are included in the IDS submitted herewith). For example, p21 only seems to affect stem cells while p27 only affects progenitor cells. Given the complexity of cell cycle regulation and the uniqueness of these cyclin-dependent kinase inhibitors, one could not be assured of the desired result until actual experiments inhibiting p21 and p27 were performed and the desired outcome observed. Merely listing other mitotic inhibitors that might be inhibited in conjunction with p27 is clearly not enough to anticipate the claimed invention in claims 4 and its dependent claims. Applicant therefore requests that the rejection be removed.

Claims 33 and 38-41 have been canceled rendering the rejection of these claims moot. Applicant requests that the rejection in view of Roberts *et al.* be removed.

II. **Rejections under 35 U.S.C. § 103.** The Examiner has rejected claims 1-45 and 75 under 35 U.S.C. § 103(a) as being unpatentable over Roberts *et al.* as applied to claims 1, 3, 4, 6-11, 13, 15-18, 20-22-29, 30, 33, 36-41, 43-45, and 75, and further in view of Waldman *et al.* (*Cancer Research* 55:5187-90, 1995). The Examiner maintains that it would have been obvious to combine the teachings of Roberts *et al.* and Waldman *et al.* to increase the proliferation of cells by disrupting both p21 and p27 in a cell population. Applicant disagrees because the references even when combined fail to teach or suggest certain features of the claimed invention. Furthermore, even if the references could be combined to support an argument that it would be obvious to try to achieve the claimed invention, there still would be no reasonable expectation of success in achieving the desired result.

The present application claims the inhibition of p21 alone or in combination with p27 to increase the proportion of proliferating cells in a population. The teachings of Roberts *et al.* are described more fully above. In sum, Roberts *et al.* does not teach the inhibition or disruption of p21 alone; therefore, the Examiner relies on the teaching of Waldman *et al.* As discussed above, Roberts *et al.* also does not specifically teach the combination of p21 and p27, but rather p21 is included in a list that includes many other mitotic inhibitors. The Examiner relies on this mere

suggestion combined with Waldman *et al.*, which teaches the disruption of the p21 genes in human colorectal cancer cell line HCT-116, to reject the listed claims.

However, even if Roberts *et al.* and Waldman *et al.* were combined, the combination could not render obvious the present claims to methods of expanding a population of cells by inhibiting *both* p21 and p27 given the lack of a reasonable expectation of success in achieving the desired result. As discussed in the last Response, Waldman *et al.* only teaches the use of a fully differentiated cancer cell line. Waldman *et al.* does not teach or suggest any method involving the use of stem or progenitor cells. The claimed invention recites stem and progenitor cells. One cannot readily extrapolate the results in fully differentiated cancer cells to undifferentiated, pluripotent cells such as stem and progenitor cells. Although the studies of Roberts *et al.* were conducted in progenitor cells, neither Roberts *et al.* nor Waldman *et al.* ever disrupted or inhibited p21 alone or in combination with p27 in a single stem or progenitor cell. The effect of cyclin-dependent inhibitor activity is unique and varies from cell to cell (*e.g.*, stem cells versus progenitor cells versus fully differentiated cells). Without such experimentation in stem or progenitor cells, there is no reasonable expectation of success in achieving the desired result of expanding a cell population. Therefore, without a reasonable expectation of success the *prima facie* case for obviousness has not been established, and Applicant requests that the rejection be removed.

Even if the independent claims are found obvious in view of Roberts *et al.* and Waldman *et al.*, the dependent claims reciting several different cell types are not. The Examiner acknowledges in the recent Office Action (p. 4) that Roberts *et al.* fail to teach erythropoietic, thrombogenic, fetal, and mesenchymal cells. The teachings of Waldman *et al.* do not make up for this deficiency since the studies in Waldman *et al.* were performed in the human colorectal cancer cell line HCT-116, and this reference suggests the use of no other cell lines. Therefore, there is no teaching or suggestion in these references to suggest many of the cell types recited in the dependent claims, and the Applicant requests that the rejection of these claims be removed.

III. **Rejections under 35 U.S.C. § 112, first paragraph.** Claims 27 and 75 stand rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. In particular, the Examiner maintains that the Specification is not enabling for antisense agents. Applicant maintains that the

use of antisense agents is enabled given the working example on pages 44-51 of the Specification. In Example 3, a lentiviral vector was used to deliver a p21 antisense agent into hematopoietic cells. The transfected cells were then shown to have decreased levels of p21 activity, and a decreased proportion of the cells in G_0 of the cell cycle was observed. Human cells transduced with a p21-antisense vector were also used to transplant irradiated NOD/SCID mice. The treatment of cells with a p21-antisense vector was found to enhance the number of stem cells, while treatment with a control vector yielded minimal engraftment. These results demonstrate the use of antisense agents in accordance with the claimed invention. For claims 27 and 75 with respect to claim 3, in which p21 alone is inhibited, these experiments are directly applicable. For claims 27 and 75 with respect to claim 6, in which both p21 and p27 are inhibited, the experiments would only need to be extended to the inhibition of p27 in addition to p21 and would not require undue experimentation by one of skill in this art given the additional guidance provided by the Specification.

A number of factors have been determined by the Federal Circuit to be useful in assessing whether the Specification provides adequate support to enable one of skill in the art to practice the claimed invention without undue experimentation. These factors include 1) the quantity of experimentation necessary; 2) the amount of direction or guidance presented; 3) the presence or absence of working examples; 4) the nature of the invention; 5) the state of the prior art; 6) the relative skill of those in the art; 7) the predictability or unpredictability of the art; and 8) the breadth of the claims. *In re Wands* 858 F.2d 731 (Fed. Cir. 1988). Applicant submits that consideration of these eight factors leads to the conclusion that the claimed invention can be practiced by one of skill in this art without undue experimentation. For example, the working example provided in the present case provides conclusive evidence that the inventors have enabled the claimed invention. The description of the working example with its experimental details and successful results provide sufficient guidance in conjunction with the description of the invention in the rest of the specification and the claims to allow one of skill in the art to practice the claimed invention. One of skill in ordinary skill in this art would be a person with a doctoral degree and post-doctoral experience in the field of molecular and cellular biology; therefore, the guidance provided by the specification is adequate for a person of such high caliber and extensive experience in the field. The claimed invention of inhibiting p21 alone or in

combination with p27 does not go beyond the teaching of the specification with its working example; therefore, no undue experimentation would be needed to practice the claimed invention. The fact that the area of anti-sense technology is considered an unpredictable art is of little consequence in light of the working example described in the specification and the high level of skill of those in this art. The claimed invention which recites the use of anti-sense agents to inhibit p21 and p27 does not extend beyond that taught by the specification and could be practiced by one of skill in this art based on the guidance provided by the specification without undue additional experimentation. Therefore, Applicant requests that the rejection for lack of enablement for the use of anti-sense agent in the claimed invention be removed.

In addition, especially with respect to claim 75, the Examiner is directed to a recent manuscript prepared by Dr. Scadden, an inventor on the present application, and others. The manuscript is entitled "Transient reduction of $p21^{Waf1/Cip1/Sdi1}$ by RNAi increases the relative number and gene transduction efficiency of human hematopoietic stem cells" and a copy of the manuscript with its accompanying figures has been included with this Response in the IDS submitted herewith. The manuscript describes the transient reduction of p21 levels in cells treated with specific RNAi constructs targeting p21. Given the successful results of inhibiting p21 activity using RNAi constructs, Applicant submits that claim 75 is enabled because based on the teaching of the Specification with regard to p21 and p27 one of ordinary skill in this art could use RNAi technology to inhibit the p21 and/or p27 activity in a cell. The Examiner is invited to contact the Applicant if these data would be useful in the form of a Declaration to overcome the instant rejection.

If it is believed that a telephone conversation would expedite matters, the Examiner is invited to contact the undersigned at (617) 248-5215. Although it is believed that there is no fee associated with this amendment, if Applicant is mistaken, please charge any fees to our Deposit Account Number: 03-1721.

Respectfully Submitted,

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